Statement of

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Mr. Chairman and members of the subcommittee, good morning, and thank you for inviting me to speak to you about the transmissible spongiform encephalopathies, referred to as TSEs. My name is Dr. Richard T. Johnson. I am a Board-certified neurologist with appointments in the Departments of Neurology, Molecular Biology and Genetics, and Neuroscience at The Johns Hopkins University School of Medicine. I also hold a joint appointment in the Department of Molecular Microbiology and Immunology at The Johns Hopkins University School of Hygiene and Public Health. My professional expertise is primarily in the fields of neurovirology, neuroimmunology, and neuropathology, and in 1986-87, I served as the primary neurology consultant for a Public Health Service interagency, epidemiological study of human growth hormone and Creutzfeldt-Jakob Disease. I am currently serving as an expert consultant to the National Institute of Neurological Disorders and Stroke and to the National Institutes of Health on the TSEs.

The TSEs are fatal neurodegenerative diseases of humans and animals. They share a characteristic brain pathology which has the appearance of "spongy" holes in the brain; a long incubation period - sometimes decades long; and the probable causative agent - proteinaceous infectious particles - known as "prions." Prions are transmissible particles that are devoid of nucleic acid and seem to be composed exclusively of a modified protein. According to the prion hypothesis, an abnormal conformation, or folding, of the normal protein carries the disease, and recruits normal prion proteins to the harmful conformation. The notion of an infectious agent that lacks the nucleic acids – the molecules which carry hereditary traits from one generation to the next and trigger the production of specific proteins – is revolutionary, but the preponderance of scientific evidence supports this hypothesis.

Animal TSEs include bovine spongiform encephalopathy, known as BSE or "mad cow disease," scrapie in sheep, and varying forms which occur in cats, mink, elk, deer, and exotic zoo animals. Creutzfeldt-Jakob disease, known as CJD, is the most common human TSE; other lesser known and rarer human forms include Fatal Familial Insomnia and Kuru. A distinct new variant form of CJD – vCJD - has been recognized only since 1996, the onset of illness in the first case having occurred in early 1994. I will briefly discuss the symptoms, incidence, and likely routes of transmission of classic CJD first, and then discuss variant CJD and its link with BSE.

In the early stages of the disease, CJD patients may have failing memory, behavior changes, impaired coordination and visual disturbances. As the illness progresses, mental deterioration becomes pronounced, and involuntary movements, blindness, weakness of extremities, and, ultimately, coma may occur. CJD usually becomes apparent in later life, and the disease typically leads to death within one year following the onset of symptoms - in the United States, the mean age of death is 67 years.

CJD, while the most common human TSE, is still very rare; it afflicts only about one in a million people each year. About 90 percent of these cases are sporadic – meaning they appear to occur spontaneously, about another ten percent are an inherited genetic disorder, and less than one percent are transmitted. The failure to find increased incidence of CJD in persons who have come into even close and regular contact with CJD patients suggests the disease is not contagious through normal routes. However, inadvertent human-to-human transmission has been reported from corneal transplantation; direct contact with contaminated medical and surgical instruments; inoculation of growth hormone prepared from contaminated cadaver pituitary glands; and grafts of dura mater - the tough fibrous membrane covering the brain and the spinal cord and lining the inner surface of the skull - obtained from cadaveric donors who had unsuspected CJD.

Variant CJD is also fatal, but is clinically and pathologically distinct from classic CJD. Clinically, vCJD patients have an earlier age of onset - mean age at death is 29 years compared to 67 years in CJD. They usually present with behavioral changes, loss of the ability to coordinate muscular movements, and peripheral sensory disturbances such as loss of sensation, rather than changes in mental activity and thinking ability, and do not show the usual brain wave activity changes of CJD. Variant CJD patients have a longer duration of illness from onset of symptoms to death - median survival is 14 months in vCJD compared to four months in CJD. Pathologically, an unusual form of plaque is present in the brains of people with vCJD: a florid or "daisy" plaque in which an amyloid core - a hard, waxy deposit that results from the degeneration of tissue - is surrounded by "petals" of spongiform change.

As of April 2, 2001, the UK has reported 97 probable or confirmed cases of deaths from vCJD since 1995, and a few more have been reported in continental Europe. No cases of vCJD have been reported in the United States. Because of the timing of the appearance of vCJD in the UK in relation to the BSE epidemic, a link between the two diseases was deemed likely. So, I will briefly discuss BSE and the evidence in support of this link, as well as the concerns it raises.

We do not know exactly how BSE, or "mad cow disease" as it frequently referred to in media reports, originated, but we do know with some certainty how it spread and reached epidemic proportions in the UK. As explored in an article in the January-February 2001 volume of the journal, *Emerging Infectious Diseases*, by Dr. Paul Brown and others, one theory for the origin of BSE is that it originated from scrapie, an endemic TSE of sheep and goats that has been recognized in Europe since the mid-18th century, and has since spread to most sheep-breeding countries. Until 1988 in the UK, the rendered carcasses of livestock, including sheep, were fed to ruminants, such as cattle, and other animals as a protein-rich nutritional supplement. Although not proven, it appears likely that changes in the UK's rendering process around 1980 allowed the causative agent in infected carcasses to survive, contaminate the protein supplement, and infect cattle. Cattle carcasses and carcass wastes were then recycled through the rendering plants, increasing the levels of the now cattle-adapted pathogen in the protein supplement and eventually causing a full-scale BSE epidemic. An alternative explanation, proposed in the recent UK "Report of the BSE Inquiry" which investigated the emergence and identification of BSE and vCJD, is that a spontaneous disease-causing mutation occurred in cattle in the 1970s. Either of these hypotheses satisfies the need for a causative agent to survive the altered rendering process, and to escalate through recycling of an ever-larger number of infected carcasses.

BSE is not restricted to the UK; cases have been reported in France, Portugal, Germany, Spain, and the Republic of Ireland, among others, probably as a result of imported live animals or livestock food supplements. However, no documented case of BSE has occurred in the United States or other countries that have historically imported little or no live cattle, beef products, or livestock nutritional supplements from the UK, even though rendering procedures in other countries underwent changes similar to those in the UK during the late 1970s.

While there were concerns about human infection resulting from the BSE epidemic, these were generally allayed by the presumption that BSE originated from scrapie, and scrapie was not a human pathogen. UK surveillance and epidemiological studies further muted these concerns. During the 10 years after the first case of BSE was identified, cases of CJD in the UK did not increase in groups at high risk, and continued to occur in the general population at the same rate and with the same spectrum of clinical and neuropathologic features as before the appearance of BSE. However, then the onset of the variant form started to appear in 1994, and the suspected link between BSE and vCJD has now been convincingly established. Laboratory studies have shown the distinctive biological and molecular features of the pathologic agent transmitted from BSE-infected cattle and human cases of vCJD to be identical. The source of transmission appears to have been beef, with infection most probably resulting from consumption of beef products contaminated by nervous system tissue.

Although the amount of infectious tissue ingested is probably a critical factor in the transmission of BSE to humans in the form of vCJD, a human genetic susceptibility in the prion protein gene - PRNP - appears to play an important role in infection. It is possible that a very specific genetic constitution, or genotype, is necessary for BSE to be able to replicate in a human as vCJD. It is also possible that certain variations of this susceptible genotype are comparatively resistant to the disease, and only become ill after longer incubation periods. As noted in Dr. Brown's recent article cited above, the difference between the incidence of BSE and vCJD may be due to limited exposure to very small infectious doses that, except in genetically susceptible persons, cannot surmount the combined effects of a species barrier – from cattle to human - and a comparatively inefficient route of infection – the digestive tract as opposed to direct central nervous system contact. On the other hand, the ultimate extent of the vCJD outbreak is unknown largely because the incubation period for vCJD is unknown.

Mr. Chairman, I know that you have an appropriately keen interest in measures being taken to prevent the occurrence and propagation of BSE in the United States. An essential aspect of any such preventive efforts is detection and diagnosis, the precision of which can only extend as far as our understanding of the nature of the disease. The NIH has a long history of research on the TSEs. This is reflected in the awarding of the

1976 Nobel Prize for intramural work begun in the 1950's that established the transmissibility of these diseases, and of the 1997 Nobel Prize for extramural work on the prion theory. Recent and ongoing studies address many aspects of TSEs and prion biology including the normal functions of the prion protein, animal models of TSEs, the molecular mechanisms of prion diseases, the role of genetics, and exploratory studies of therapeutic strategies. Finally, a major contract effort is working to develop presymptomatic tests.

This concludes my testimony. I would be pleased to respond to any questions you might have.

Appendix:

Paul Brown, Robert G. Will, Raymond Bradley, David M. Asher, and Linda Detwiler, "Bovine spongiform encephalopathy and variant Creutzfeldt-Jakob disease: background, evolution, and current concerns." Emerg Infect Dis. 2001 Jan-Feb;7(1):6-16.